

Variant: *NM_000527.5(LDLR):c.269A>C (p.Asp90Ala)*

Version: 1.0

CA404075695 [↗](#)

440555 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: 484e1059-d6ac-4816-9757-dbdb0ed3bed2

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HGVS expressions

NM_000527.5(LDLR):c.269A>C (p.Asp90Ala)

NM_000527.5:c.269A>C

NC_000019.10:g.11102742A>C

CM000681.2:g.11102742A>C

NC_000019.9:g.11213418A>C

CM000681.1:g.11213418A>C

NC_000019.8:g.11074418A>C

NG_009060.1:g.18362A>C

ENST00000252444.10:c.527A>C

ENST00000559340.2:c.269A>C

ENST00000560467.2:c.269A>C

ENST00000558518.6:c.269A>C

ENST00000252444.9:c.523A>C

ENST00000455727.6:c.269A>C

ENST00000535915.5:c.190+2397A>C

ENST00000545707.5:c.269A>C

ENST00000557933.5:c.269A>C

ENST00000557958.1:n.355A>C

ENST00000558013.5:c.269A>C

ENST00000558518.5:c.269A>C

NM_000527.4:c.269A>C

NM_001195798.1:c.269A>C

NM_001195799.1:c.190+2397A>C

NM_001195800.1:c.269A>C

NM_001195803.1:c.269A>C

NM_001195798.2:c.269A>C

NM_001195799.2:c.190+2397A>C

NM_001195800.2:c.269A>C

NM_001195803.2:c.269A>C

Likely Pathogenic

Met criteria codes **4**

PM2

PM5_Strong

PP3

PP4

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PM1

PM3

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

PS3

PS4

BP5

BP7

BP4

BP3

BP1

BP2

BA1

PP1

PP2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel			
Familial Hypercholesterolemia VCEP			
The NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM5_Strong, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PM5_Strong - 4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There are 3 variants classified as Pathogenic by these guidelines, so PM5_Strong is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PP3 - REVEL = 0.964. It is above 0.75, so PP3 is met PP4 - Variant meets PM2, and was identified in 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an early age, and the presence of primary hypercholesterolemia in the probands’ parents or other first degree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA so PP4 is met			
Met criteria codes			
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met
PM5_Strong			4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There are 3 variants classified as Pathogenic by these guidelines, so PM5_Strong is met.
PP3			REVEL = 0.964. It is above 0.75, so PP3 is met
PP4			Variant meets PM2, and was identified in: - 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an early age, and the presence of primary hypercholesterolemia in the probands’ parents or other firstdegree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA so PP4 is met
Not Met criteria codes			
PM1			Variant is not in exon 4 and does not alter Cys, so not met
PM3			Variant meets PM2, but there are no case data

PM4			variant is missense, so not met
PM6			no case data
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
BS4			no case data
BS3			no functional study performed
BS2			no case data
PVS1			variant is missense and not in initiation codon, so not met
PS1			no other variant leads to the same amino acid change in the same codon, so not met
PS2			no case data
PS3			no functional study performed
PS4			Variant meets PM2, and was identified in: - 1 index case with SB criteria for FH (The clinical diagnosis of hoFH was confirmed on the basis of total cholesterol >500 mg/dl at the time of diagnosis, the presence of xanthomas at an early age, and the presence of primary hypercholesterolemia in the probands' parents or other firstdegree relatives. This case had total cholesterol 840mg/dl at 3 years of age) from PMID 19026292 (Kolansky et al., 2008), USA not enough, so not met
BP5			not applicable
BP7			variant is missense, so not met
BP4			REVEL = 0.964. It is not below 0.50, so not met
BP3			not applicable
BP1			not applicable
BP2			no case data
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met

PP1			no case data
PP2			not applicable

Curation History 			
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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.